09-29-00 A/RE

jc759 U.S. PTO 09/28/00

jc917 U.S. PTO 09/672843 09/28/00

Please type a plus sign (+) inside this box → +

PTO/SB/50 (08-00)
Approved for use through 12/30/2000. OMB 0651-0033
U S Patent and Trademark Office, U S DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

REISSUE PATENT APPLICATION TRANSMITTAL

Address to:

Assistant Commissioner for Patents
Box Reissue
Washington, DC 20231

Attorney Docket No.	14127.0001U1
First Named Inventor	Lee G. Dante
Original Patent Number	6,034,091
Original Patent Issue Date (Month/Day/Year)	March 7, 2000
Express Mail Label No.	EL403201815US

APPLICATION FOR REISSUE OF: (Check applicable box) [X] Utility Patent [ ] Design Patent [ ] Plant Patent

APPLICATION ELEMENTS (37 CFR 1.173)

1. [X] Fee Transmittal Form *(PTO/ SB/ 56)* (Submit an original, and a duplicate for fee processing)
2. [ ] Applicant claims small entity status. See 37 CFR 1.27.
3. [X] Specification and Claims in double column copy of patent format *(amended, if appropriate)*
4. [ ] Drawing(s) *(proposed amendments, if appropriate)*
5. [X] Reissue Oath/Declaration (original or copy) *(37 C.F.R. § 1.175) (PTO/SB/51 or 52)*
6. Original U.S. Patent currently assigned?

   [X] Yes [ ] No

   (If Yes, check applicable boxes))

   [X] Written Consent of all Assignees *(PTO/SB/53)*

   [X] 37 C.F.R. § 3.73(b) Statement (PTO/SB/96) [ ] Power of Attorney

ACCOMPANYING APPLICATION PARTS

7. [X] Statement of status/support for all changes to the claims. See 37 CFR 1.173 (c).
8. [ ] Original U.S. Patent for surrender
   - [ ] Ribboned Original Patent Grant
   - [ ] Statement of Loss (PTO/SB/55)
9. [ ] Foreign Priority Claim *(35 U.S.C. 119) (if applicable)*
10. [ ] Information Disclosure Statement (IDS)/PTO-1449 [ ] Copies of IDS Citations
11. [ ] English Translation of Reissue Oath/Declaration *(if applicable)*
12. [X] Preliminary Amendment
13. [X] Return Receipt Postcard *(MPEP 503) (Should be specifically itemized)*
14. Other: .....

15. CORRESPONDENCE ADDRESS

[X] Customer Number or Bar Code Label (Insert Customer No. or Attach bar code label here) or [ ] Correspondence address below

Name	23859 PATENT TRADEMARK OFFICE				
Address					
City		State		Zip Code	
Country		Telephone		Fax	

NAME (Print/Type)	William R. Johnson	Registration No. (Attorney/Agent)	32,875
Signature		Date	9-28-00

Burden Hour Statement This form is estimated to take 0.2 hours to complete Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U S Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS SEND TO Assistant Commissioner for Patents, Box Reissue, Washington, DC 20231.

PTO/SB/56 (08-00)
Approved for use through 12/30/2000 OMB 0651-0033
U.S Patent and Trademark Office, U S DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

REISSUE APPLICATION FEE TRANSMITTAL FORM

Docket Number (Optional): 14127.0001U1

Claims as Filed - Part 1

Claims in Patent		Number Filed in Reissue Application	(3) Number Extra	Small Entity Rate	Small Entity Fee		Other than a Small Entity Rate	Other than a Small Entity Fee
(A) 7	Total Claims (37 CFR 1.16(j))	(B) 25	**** 5 =	x $____ =		or	x $18 =	90
(C) 1	Independent claims (37 CFR 1.16(i))	(D) 4	* 3 =	x $____ =			x $79 =	234
				Basic Fee (37 CFR 1.16(h))	$____			$ 690
				Total Filing Fee	$		OR	$ 1,014

Claims as Amended - Part 2

	(1) Claims Remaining After Amendment		(2) Highest Number Previously Paid For	(3) Extra Claims Present	Small Entity Rate	Small Entity Fee		Other than a Small Entity Rate	Other than a Small Entity Fee
Total Claims (37 CFR 1.16(j))	***	MINUS	**	* =	x $____ =			x $____ =	
Independent Claims (37 CFR 1.16(i))	***	MINUS	*****	=	x $____ =			x $____ =	
					Total Additional Fee	$		OR	$

* If the entry in (D) is less than the entry in (C), Write "0" in column 3.

** If the "Highest Number of Total Claims Previously Paid For" is less than 20, Write "20" in this space.

*** After any cancellation of claims.

**** If "A" is greater than 20, use (B - A); if "A" is 20 or less, use (B - 20).

***** "Highest Number of Independent Claims Previously Paid For" or Number of Independent Claims in Patent (C).

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ Please charge Deposit Account No. _____ in the amount of _____.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any additional fees under 37 CFR 1.16 or 1.17 which may be required, or credit any overpayment to Deposit Account No. 14-0629.
A duplicate copy of this sheet is enclosed.

☒ A check in the amount of $ 1,014.00 to cover the filing / additional fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

Sept. 28, 2000
Date

Signature of Applicant, Attorney or Agent of Record

William R. Johnson
Typed or printed name

Burden Hour Statement This form is estimated to take 0 2 hours to complete Time will vary depending upon the needs of the individual case Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U S Patent and Trademark Office, Washington, DC 20231 DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

PTO/SB/96 (6-98)
Approved for use through 09/30/2000. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: John S. Nagle

Application No./Patent No.: 6,034,091 Filed/Issue Date: March 7, 2000

Entitled: Method for Treating Emotional or Mental Illness and Emotional or Mental Illness Concomitant with Seizures

John S. Nagle, a Individual,
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. [ ] the assignee of the entire right, title, and interest; or

2. [X] an assignee of an undivided part interest

in the patent application/patent identified above by virtue of either:

A. [X] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the Patent and Trademark Office at Reel 7663, Frame 0447, or for which a copy thereof is attached.

OR

B. [ ] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as shown below:

1. From: _____ To: _____
The document was recorded in the Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____
The document was recorded in the Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____
The document was recorded in the Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet.

[ ] Copies of assignments or other documents in the chain of title are attached.
[NOTE: A separate copy (i.e., the original assignment document or a true copy of the original document) must be submitted to Assignment Division in accordance with 37 CFR Part 3, if the assignment is to be recorded in the records of the PTO. See MPEP 302-302.8]

The undersigned (whose title is supplied below) is empowered to sign this statement on behalf of the assignee.

9-18-00
Date

Signature

John S. Nagle
Typed or printed name

Assignee
Title

PTO/SB/53 (12-97)
Approved for use through 9/30/00. OMB 0651-0033
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

REISSUE APPLICATION BY THE INVENTOR, OFFER TO SURRENDER PATENT	Docket Number (Optional) 14127.0001U1

This is part of the application for a reissue patent based on the original patent identified below.

Name of Patentee(s)
Lee G. Dante

Patent Number	Date Patent Issued
6,034,091	March 7, 2000

Title of Invention: Method for Treating Emotional or Mental Illness and Emotional or Mental Illness Concomitant with Seizures

I am the inventor of the original patent.

I offer to surrender the original patent.

1. [x] Filed herein is a certificate under 37 CFR 3.73(b).

2. [ ] Ownership of the patent is in the inventor(s), and no assignment of the patent has been made.

One of boxes 1 or 2 above must be checked.

The written consent of all assignees owning an undivided interest in the original patent is included in this application for reissue.

Signature	Date

Typed or printed name
Lee G. Dante

The assignee owning an undivided interest in said original patent is John S. Nagle, and the assignee consents to the accompanying application for reissue.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application, any patent issued thereon, or any patent to which this declaration is directed.

Name of assignee
John S. Nagle

Signature of person signing for assignee	Date
John S. Nagle	9-18-00

Typed or printed name and title of person signing for assignee
John S. Nagle

Burden Hour Statement: This form is estimated to take 0.1 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

PTO/SB/53 (12-97)
Approved for use through 9/30/00. OMB 0651-0033
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

REISSUE APPLICATION BY THE INVENTOR, OFFER TO SURRENDER PATENT

Docket Number (Optional): 14127.0001U1

This is part of the application for a reissue patent based on the original patent identified below.

Name of Patentee(s)
Lee G. Dante

Patent Number	Date Patent Issued
6,034,091	March 7, 2000

Title of Invention: Method for Treating Emotional or Mental Illness and Emotional or Mental Illness Concomitant with Seizures

I am the inventor of the original patent.

I offer to surrender the original patent.

1. [X] Filed herein is a certificate under 37 CFR 3.73(b).

2. [ ] Ownership of the patent is in the inventor(s), and no assignment of the patent has been made.

One of boxes 1 or 2 above must be checked.

The written consent of all assignees owning an undivided interest in the original patent is included in this application for reissue.

Signature	Date
Lee G. Dante	9/18/00

Typed or printed name
Lee G. Dante

The assignee owning an undivided interest in said original patent is John S. Nagle, and the assignee consents to the accompanying application for reissue.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application, any patent issued thereon, or any patent to which this declaration is directed.

Name of assignee
John S. Nagle

Signature of person signing for assignee	Date

Typed or printed name and title of person signing for assignee
John S. Nagle

ATTORNEY DOCKET NO. 14127.0001U1
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Reissue of)
)
Lee G. Dante)
)
Serial No. 09/165,549)
Patent No. 6,034,091)
)
Filed: October 2, 1998)
Issued: March 7, 2000)

For: METHOD FOR TREATING EMOTIONAL OR MENTAL ILLNESS AND EMOTIONAL OR MENTAL ILLNESS CONCOMITANT WITH SEIZURES

PRELIMINARY AMENDMENT IN REISSUE AND REQUEST FOR INTERFERENCE

BOX REISSUE APPLICATION
Assistant Commissioner for Patents
Washington, D.C. 20231

NEEDLE & ROSENBERG, P.C.
Suite 1200, The Candler Building
127 Peachtree Street, N.E.
Atlanta, Georgia 30303-1811

September 28, 2000

Sir:

Prior to examination on the merits, please amend the above-identified reissue application as follows:

IN THE CLAIMS

Kindly add the following new claims 8-25:

8. A method of treating alcoholism and depression associated therewith comprising administering to a patient an effective amount of an opioid antagonist selected from the group consisting of nalmefene, naltrexone, nalmefene, nalorphine, nalbuphine, thebaine, levallorphan, oxymorphone, butorphanol, buprenorphine, levorphanol, meptazinol, pentazocine, dezocine, and their pharmacologically effective esters and salts, and an effective amount of an antidepressant, which antidepressant is selected from the group consisting of imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, clomipramine, maprotiline, and carbamazepine and bupropion, sertraline, fluoxetine, trazodone, and their pharmacologically effective esters and salts.

9. The method according to claim 8 wherein the opioid antagonist is naltrexone administered in an amount of from 10 to 150 mg.

10. The method according to claim 9 wherein the antidepressant is fluoxetine administered in an amount not greater than 80 mg.

11. The method according to claim 10 wherein fluoxetine is administered in an amount of from 20 to 80 mg.

12. The method according to claim 9 wherein fluoxetine is administered in a dosage of between 10 and 40 mg.

13. The method according to claim 8 wherein the opioid antagonist is naltrexone in an amount of 10 to 25 mg and the antidepressant is fluoxetine in an amount less than 20 mg.

14. A pharmaceutical composition comprising a pharmalogically effective amount of an opioid antagonist selected from the group consisting of nalmefene, naltrexone, nalmefene, nalorphine, nalbuphine, thebaine, levallorphan, oxymorphone, butorphanol, buprenorphine, levorphanol, meptazinol, pentazocine, dezocine, and their pharmacologically effective esters and salts, and a pharmalogically effective amount of an antidepressant, which antidepressant is selected from the group consisting of imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, clomipramine, maprotiline, and carbamazepine and bupropion, sertraline, fluoxetine, trazodone, and their pharmacologically effective esters and salts.

15. The pharmaceutical composition according to claim 14 wherein the opioid antagonist is naltrexone in an amount of 10-150 mg.

16. The composition according to claim 15 wherein the antidepressant is fluoxetine in an amount of 20-80 mg.

17. The component according to claims 15 wherein the antidepressant is fluoxetine in an amount of fluoxetine is 10-40 mg.

18. The composition according to claim 14 wherein the opioid antagonist is naltrexone present in an amount of 10-25 mg and the antidepressant is fluoxetine present in an amount less than 20 mg.

19. The pharmaceutical composition according to claim 14 wherein in opioid antagonist is nalmefene.

20. The pharmaceutical composition according to claim 14 wherein the antidepressant is sertraline.

21. A pharmaceutical kit comprising an effective pharmaceutical amount of an opioid antagnoist selected from the group consisting of nalmefene, naltrexone, nalmefene, nalorphine, nalbuphine, thebaine, levallorphan, oxymorphone, butorphanol, buprenorphine, levorphanol, meptazinol, pentazocine, dezocine, and their pharmacologically, effective esters and salts, and an effective pharmacentral amount of an antidepressant, which antidepressant is selected from the group consisting of imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, clomipramine, maprotiline, and carbamazepine and bupropion, sertraline, fluoxetine, trazodone, and their pharmacologically effective esters and salts.

22. The pharmaceutical kit according to claim 21 wherein an opioid antagonist is naltrexone present in an amount of 10-150 mg.

23. The pharmaceutical kit according to claim 22 wherein the antidepressant is fluoxetine present in the amount of 20-80 mg.

24. The pharmaceutical lab according to claim 22 wherein the antidepressant is fluoxetine present in more than one dosage, each dosage having an amount of 10-40 mg.

25. The pharmaceutical kit according to claim 21 wherein the opioid antagnoist is naltrexone present in the amount of 10-25 mg, and the antidepressant is fluoxetine present in the amount less than 20 mg.

REMARKS

By the present amendment, new claims 8-25 have been introduced in order to provoke an interference with U.S. Patent 5,958,962.

I. NEW CLAIMS 8-21

Support for the newly added claims can be found throughout the application. For example, descriptive support for a method of treating alcoholism together with depression, as recited in Claim 8, can be found at least in Example 4 of the patent. See, e.g., column 6, lines 59-60.

Example 1 appearing in column 5 provides descriptive support for providing separate treatments of the antagonist and depressant. See, e.g., column 5, lines 61-63. Accordingly, this example provides adequate written descriptive support for a "kit" claim such as that of new claims 21-25.

The use of naltrexone as well as the claimed amount of 10-150 mg/day is found at column 3, lines 14-17 and 34-36. As to the use of naltrexone in an amount of 10-25 mg/day, attention is directed towards the disclosure at column 4, lines 37-44, as well as claims 3 and 4 of the patent.

Support for the use of fluoxetine as the antidepressant can be found at least at column 5, line 12 of the specification. Moreover, descriptive support for the claimed amounts of fluoxetine can be

found at least in column 2, lines 4-9 and column 3, lines 25-33 which incorporates portions of the Physician Desk Reference (PDR) by reference. A copy of the PDR disclosure relating to fluoxetine is being filed concurrently herewith.

In looking at the PDR disclosure concerning fluoxetine, attention is directed toward the "Description" section appearing on page 943, and the "Dosage And Administration" and "How Supplied" sections appearing on page 947 of the PDR. In particular, the "Depression" subsection of the "Dosage And Administration" section sets forth a maximum recommended dosage of 80 mg, as well as a recommended dosage of 20-80 mg. It further discloses that doses greater than 20 mg may be given twice a day, corresponding to 10-40 mg dosages. Finally, the fourth paragraph of the "Depression" subsection states that a "lower" dosage should also be considered for patients on "multiple medications."

Accordingly, the PDR, which is incorporated by reference into the Dante patent, provides descriptive support for all of the numerical recitations involving fluoxetine in claims 8-25.

No new matter has been introduced by these new claims.

II. REQUEST FOR INTERFERENCE

In accordance with the provisions of 37 C.F.R. § 1.607, Applicants also request that an interference be declared between this reissue application and unexpired U.S. Patent 5,958,962.

In accordance with the provisions of 37 C.F.R. §1.607(a), Applicants offer the following:

(1) The patent in question is U.S. Patent 5,958,962 which issued September 28, 1999;

(2) The proposed count is as follows:

Claims 1, 2 or 3 of U.S. Patent 5,958,962

or Claim 1, 8, 14 or 21 of this reissue application;

(3) Each of claims 1-3 of U.S. Patent 5,958,962 correspond to the proposed count;

(4) Each of claim 1-25 of this reissue application correspond to the proposed count.

As to 37 C.F.R. §1.608, the effective filing date of the present reissue application, March 2, 1993, is **more than 18 months earlier** than the effective filing date of U.S. Patent 5,958,962, September 19, 1994. Accordingly, it is submitted that **no** showing under 37 C.F.R. §1.608 is required.

An early declaration of interference is in order and such action is earnestly solicited.

As a final matter, should the examiner have any questions regarding this paper, or the reissue application in general, he/she is invited to telephone the undersigned at his/her earliest convenience.

Respectfully submitted,

William R. Johnson
Registration No. 32,875

Suite 1200, The Candler Building
127 Peachtree Street, N.E.
Atlanta, Georgia 30303-1811
(404) 688-0770

CERTIFICATE OF EXPRESS MAILING UNDER 37 C.F.R. §1.10

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail, No. EL403201815US in an envelope addressed to: Assistant Commissioner for Patents, BOX REISSUE APPLICATION, Washington, D.C. 20231, on this 28th day of September, 2000.

Evelardo McFarlane

9-28-00
Date

METHOD FOR TREATING EMOTIONAL OR MENTAL ILLNESS AND EMOTIONAL OR MENTAL ILLNESS CONCOMITANT WITH SEIZURES

This application is a continuation of Ser. No. 08/755,795, filed Aug. 28, 1996, now U.S. Pat. No. 5,856,332, which is a divisional of Ser. No. 08/560,820, filed Nov. 20, 1995, now U.S. Pat. No. 5,817,665, which is a divisional of Ser. No. 08/031,096, filed Mar. 2, 1993, now U.S. Pat. No. 5,512,593.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to the use of an opioid antagonist such as naltrexone in combination with one or more serotonin (5-hydroxytryptamine or 5-HT) or norepinephrine reuptake inhibitor(s) and/or lithium to treat mental or emotional disorders characterized by depression, obsessiveness, depression with anxiety, mania, manic depression, depression with manic episodes, and depression concomitant with an illness causing seizures which are inhibited by carbamazepine, or a combination of any of these mental or emotional illnesses, or mental or emotional illnesses with seizures. The inventor has discovered that naltrexone is useful in combination with lithium and/or one or more serotonin (5-HT) uptake inhibitor and/or norepinephrine (N.E.) uptake inhibitor drug compounds in treating patients whose depression and/or associated mental illnesses or conditions were refractory to drug treatment using one or more known antidepressant agents or agents for manic and manic depressive disorders such as lithium, and tricyclic and a-typical antidepressants including, but not limited to clomipramine, amitriptyline, imipramine, sertraline and nortriptyline that inhibit 5-HT and/or N.E. reuptake.

The inventor has further discovered that such treatment using naltrexone in combination with lithium and/or 5-HT or N.E. reuptake inhibitors is effective even where benzodiazepines are concurrently administered to treat anxiety. Additionally, the inventor has discovered that lithium in combination with naltrexone in some cases reduces manic and manic depressive bipolar symptoms.

DESCRIPTION OF THE RELATED PRIOR ART

A general discussion of the effectiveness of tricyclic antidepressants and non-tricyclic a-typical antidepressants in inhibiting 5-HT and/or N.E. neuronal synaptic reuptake and in treating depression, along with the pharmacology of these compounds is found in Goodman and Gillman, *The Pharmacological Basis of Therapeutics*, 7th and 8th Eds. (MacMillan Publ. Co.) Chapt. 19, Section 11 "Drugs Used in the Treatment of Disorders of Mood", incorporated by reference herein. According to the present invention, tricyclic antidepressants include, but are not limited to, imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, clomipramine, maprotriline, and carbamazepine, and their pharmaceutically effective salts and esters, such as, but not limited to their hydrochlorides, maleates, tartrates and lactates. Although carbamazepine is approved in the U.S. as antiepileptic, it is chemically related to tricyclic antidepressants, its actions on human brain neurons are not completely known, and for the present invention it is classified as a tricyclic antidepressant. See, Goodman and Gillman, *The Pharmacological Basis of Therapeutics*, referenced above, 7th Ed., page 457 et seq.

According to the present invention, a-typical antidepressants include, but are not limited to, bupropion, sertraline,

fluoxetine, and trazodone and their pharmacologically effective salts and esters, such as, but not limited to, their hydrochlorides, maleates, tartrates and lactates.

Additional discussion of these drug compounds and their analogs' pharmacologic action in inhibiting 5-HT and N.E. and in treating depression is found in the *Physician's Desk Reference* (PDR), 47th Ed., 1993, published by Medical Economics Co., Inc., Montvale, N.J., indexed by generic compound name and incorporated by reference herein.

The opioid antagonists which may be employed in the present invention have been known for use in treatment of opioid overdose and to prevent abuse of opioids such as heroin or morphine. The pharmacology of opioid antagonist compounds are described in Goodman and Gillman, *Pharmacological Basis of Therapeutics,* 7th & 8th Eds. (as noted above), Chapt. 22, "Opioid Antagonists", incorporated by reference herein, and include, but are not limited to cyclazocine, naloxone, opioid antagonist compounds having the same pentacyclic nucleus as nalmefene, naltrexone, nalmefene, nalorphine, nalbuphine, thebaine, levallorphan, pentazocine, oxymorphone, butorphanol, buprenorphine, levorphanol, meptazinol, dezocine, and pentazocine and their pharmacologically effective salts and esters such as, but not limited to their hydrochlorides, maleates, tartrates and lactates.

The generally accepted use for opioid antagonists in treatment of human ailments has been for reversing opioid toxicity and overdoes, and in preventing abuse of opioids, such as heroin and morphine. However, Glover, in U.S. Pat. No. 5,028,612 incorporated by reference herein, discusses use of opioid antagonists, such as naltrexone, in a method for treating emotional numbness where emotional numbness is "conceptualized as a biopsychological response to extreme emotional or physical trauma" and is featured by a person's subjective experience of inability to feel emotions, and lack of care and concern for others.

Glover also discloses that naltrexone may be used in treatment of emotional numbness coupled with other emotional disorders, such as post traumatic stress syndrome, schizophrenia, depression, anxiety, hypochondria, and psychomotor disorders, although no support for success in treating such patients is disclosed.

Horrobin in U.S. Pat. No. 4,388,324 discloses a method of moderating the effects of taking alcohol by administering, among other compositions, a composition of γ-linolenic acid and/or ascorbic acid and/or ethyl alcohol and/or opioid antagonist (See, col. 7, lines 30–35). Horrobin discloses that endogenous opioid excess, suspected in schizophrenia, coeliac diseases and psoriasis may be reversed by opioid antagonists such as naloxone (See, U.S. Pat. No. 4,388,32, col. 3, lines 15–19).

SUMMARY OF THE INVENTION

In many cases of profound depression, tricyclic and a-typical antidepressants and lithium do not provide sufficient relief to patients so as to prevent suicide ideation or allow the patient to successfully carry out continuous daily work routines and social routine activities. In some cases of endogenous depression, reactive depression, and in some cases where patients exhibit depression without suicide ideation, tricyclic and a-typical antidepressants and lithium do not satisfactorily control patient symptoms or condition.

It is an object of the present invention to provide a novel method for treating depression, obsessiveness, depression with obsessiveness, depression with anxiety, mania, depression associated with bipolar conditions such as manic

depression, depression with manic episodes, and depression concomitant with an illness causing seizures which are inhibited by carbamazepine, or a combination of these mental or emotional illnesses. These mental or emotional illnesses to be treated may or may not be successfully treatable with a tricyclic or a-typical antidepressants or lithium or a benzodiazepine with anti-anxiety activity or a combination of these agents without concomitant opioid antagonist administration. The novel method of treatment is accomplished by adding an opioid antagonist drug compound to the drug treatment regimen for emotional or mental illness or emotional or mental illness concomitant with an illness causing seizures. Preferably, the opioid antagonist added to the treatment regimen is naltrexone (Trexan) given in an amount of 10–150 mg. per day, along with other medication for depression and/or manic or bipolar disorder.

It has further been determined that such a drug combination using an opioid antagonist or partial antagonist decreases the craving for sugars and carbohydrates often experienced with conventional tricyclic and a-typical antidepressant therapy.

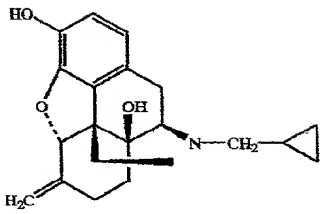
The amounts of tricyclic or a-typical antidepressant or lithium which may be used with opioid antagonist to achieve the invention are dosage amounts typically given in treatment of depression, mania, or manic depression bipolar conditions well known to physicians treating mental or emotional conditions and to pharmacists, pharmacologists, and those skilled in the art, and further are those as directed by the labelling for these drugs as found in the 1993 PDR. The amount of opioid antagonist to be administered should be tailored to individual patient needs but generally is in the range of 10–150 mg/day. However, larger doses may be given if tolerated well by the patient, as needed. Appropriate and safe dosages for opioid antagonists are generally discussed in the PDR for each opioid antagonist and in Goodman and Gillman, *Pharmacological Basis of Therapeutics*, referenced above, and also may be determined on a molar weight basis equivalent to that for 10–150 mg. of naltraxone (Trexan).

The tricyclic antidepressants which may be used in the present invention include, but are not limited, to imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, clomipramine, maprotiline, and carbamazepine and their pharmaceutically effective salts and esters.

The a-typical antidepressants which may be used in the present invention include, but are not limited to, bupropion, sertraline, fluoxetine, trazodone, and their pharmacologically effective esters and salts.

The opioid antagonist which may be used in the present invention include, but are not limited to, naloxone, opioid antagonist having the same pentacyclic nucleus as nalmefene, naltrexone, nalmefene, nalorphine, nalbuphine, thebaine, levallorphan, oxymorphone, butorphanol, buprenorphine, levorphanol, meptazinol, pentazocine, dezocine, and their pharmacologically effective esters and salts.

The pentacyclic nucleus is exemplified in the structural formula for nalmefene shown below:



The opioid antagonist to be used in the invention may also possess some opioid agonist activity, and thus may be a partial antagonist with some agonist activity (partial agonist activity).

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention relates to the use of opioid antagonists in combination with lithium and/or a tricyclic antidepressant and/or an a-typical antidepressant with and without concomitant administration of an anti-anxiety agent such as a benzodiazepine to treat emotional or mental illness or emotional or mental illness concomitant with an illness causing seizures.

It has been discovered that such a treatment results in remarkable alleviation of patients' suicide ideation and general depressed state or mania where such depressed or manic condition was refractive to treatment without opioid antagonist but with lithium and/or a tricyclic antidepressant and/or an a-typical antidepressant.

Preferably, in the present invention, the patient is given a dose of 25 or 50 mg. of Trexan per day in the morning, depending on the size of the patient and the severity of the symptoms of depression.

Some patients may experience several days of sleepiness when Trexan is used in combination with tricyclic or a-typical antidepressants and in these patients an alternative dose would be in the neighborhood of 10 mg taken at bedtime for the first three days of administration. On the fourth day, 10 mg may be administered and assuring that no sleepiness is evident the dose should be advanced to 25 mg. each morning for the next four weeks. In some individuals, especially those experiencing seasonal depressions, administration at night may be more effective and that effect would be noted within a few days of switching the time of administration following the first month of treatment. After one month of treatment, some individuals showing a response to the psychotropic medicine that is being given concurrently may get a response by increasing the dose of the opioid antagonist. In the case of Trexan, a dose of 50 mg. has been effective in getting response to develop.

A number of adverse effects of the administration of psychotropics have been observed to diminish upon this combination therapy, most notably the weight gain associated with long term administration of tricyclics. The effect of using opioid antagonists to augment treatment with psychotropic medications is not restricted to depressive disorders as attenuation of hostility and irritability by antidepressant medications has been enhanced as well as the reduction in anxiety states and obsessive compulsive states. The facilitation of effect is not restricted to those who are non-responsive to psychotropic agents but has been observed in those who have had responses which, while satisfactory to the patient, were many times improved upon augmentation with the opioid antagonist.

The patients whose treatment with antidepressants are to be supplemented by benzodiazepine medication experience a dramatic decrease in their requirement for those categories of medication upon successful combination of the antidepressant being taken with naltrexone. In several cases studied, treatment with the opioid antagonist alone was completely unsatisfactory as was treatment with the psychotropic medication by itself. This phenomena has been noted with amitriptyline (Elavil), clomipramine (Anafranil), imipramine (Tofranil), and sertraline hydrochloride (Zoloft) and Lithium. Promising results have also been obtained with carbamazepine (Tegretal), and fluoxetine (Prozac).

Patients should be warned about not stopping benzodiazepine medicines such as alprazolam (Xanax) or lorazepam (Ativan) without supervision otherwise their perception of not needing the effects of these anti-anxiety agents may lead them to stop too abruptly and precipitate withdrawal symptoms. Occasionally, in the first three to five days of administration, patients describe customarily pleasant dreams replaced by anxious or irritable dreams. This phenomena subsides after a few days.

The invention will be more fully understood by reference to the following examples.

EXAMPLE 1

A woman in her thirties who had a long history of depression treatment failure requested new treatment. She had, at various times, been bulimic, self-mutilating, alcoholic, and subject to obsessive thoughts. She had recurrent major depressive episodes which included characteristic vegetative signs of disturbed sleep, decreased appetite, energy, ability to concentrate and remember as well as the affective symptoms of sadness, irritability, and intense anxiety. At the time new treatment was begun, she presented symptoms of depression and insomnia. A variety of antidepressants were tried, the last being clomipramine hydrochloride (Anafranil), approved as an anti-obsessive drug in the U.S. but a quite effective antidepressant in use in other countries for many years. At a dose of 200 mg. Anafranil at bedtime, she got a very minimal lifting of depression but was able to sleep. Months later, she presented, having discontinued the Anafranil some time before but then noted a return of increased depression and insomnia.

Restarting the Anafranil improved her sleep but little else. Trexan was added at a dose of 50 mg. daily in the morning and from three to five weeks after beginning this regimen, she noted a dramatic lifting of the depression.

After a period on full doses of Anafranil, Anafranil was slowly withdrawn stopping at 50 mg. of the antidepressant at night. She had a moderate reduction in mood but insisted that she still had an impressive result compared to post-treatment.

The Trexan was given at night instead of in the morning and she experienced an immediate return of depression and of special note, a return of what she described as obsessive thoughts and behaviors. Reinstatement of the Trexan in the morning resulted in immediate return of the ameliorative effect on depression and the cessation of obsessive thinking.

The patient was returned to treatment with 150–200 mg. Anafranil at night and 50 mg. Trexan in the morning with good results.

EXAMPLE 2

An obese woman in her thirties who had been hospitalized for recurrent major depressive symptoms requested treat-

ment. She also had vegetative signs and was frequently suicidal. She was treated with large doses of amitriptyline (Elavil), fluoxetine hydrochloride (Prozac) and eventually sertraline hydrochloride (Zoloft) with marginal effects. She then took a lethal overdose of amitriptyline which she surprisingly survived. During her last hospital stay, a stimulant, Ritalin, was added in doses up to 160 mg. daily because of her lifelong distractibility and school difficulties consistent with Attention Deficit Disorder. She felt markedly better on Ritalin plus Zoloft 150 mg. in the morning but still complained of craving for sweets, a frequent side effect of antidepressant therapy which in her case resulted in 100 lb., plus, weight gain. She was also taking substantial doses of alprazalom (Xanax). The combination allowed her to be out of a hospital and reasonably non-suicidal.

She was started on Trexan, 25 mg., in the morning without making any other changes. Very rapidly she lost her craving for sweets and a weight loss effort which was stalled took off. She lost thirty pounds in three weeks. After three weeks of Trexan augmentation she started to feel "Happy" and without prompting she discontinued all use of Xanax. The dosage of Ritalin was then reduced. While on combination therapy of Zoloft, Ritalin and Trexan, the patient has had no suicide ideation and continues to report being happy.

The loss of a carbohydrate craving is also of note as this is one of the most prominent causes of non-compliance in depressed patients. She was maintained with Zoloft, Ritalin, and Trexan 50 mg. dosing in the morning.

EXAMPLE 3

An obese man with a history of chronic recurrent depressive episodes especially characterized by explosive rage and a pervasive irritability requested treatment. He had racing thoughts and frequent swings in energy. In addition, he was subject to distractibility going back through early childhood. His diagnosis was Bipolar Mood Disorder, type 2. He responded to Amitriptyline 200 mg. at bedtime augmented by Lithium Carbonate up to 900 mg. daily. He was pleased with his result noting diminishing anger, better self control and was willing to live with the craving for sweets which treatment brought out despite gaining about 80 lbs. Then, 25–50 mg. of Trexan was added to his medicines taken in the morning and again after three to four weeks he noted a dramatically better mood.

He reported, "This is strange. All my life I've been suspicious and have looked at things expecting the worst. I have always been negative. Now I'm looking at things positively and it feels weird." He commented that he no longer craved sweets and reported losing about 10 lbs. a week. He said that his mood swings were gone and his anger was completely gone. This result was dramatically different than what was evident before the Trexan was added. He was then fired in a corporate downsizing and reported that he did not understand why he was just calmly going about the transition rather than falling apart.

EXAMPLE 4

A recovering alcoholic about age sixty with a major depression requested new treatment. He commented that he had not been happy for at least twenty five years. He was started on Zoloft, 50 mg. in the morning and 10, 50 mg. Trexan tablets with the instruction to take 25 mg. each morning until he ran out. He had been taking lorazepam (Ativan) a 5 mg. four times a day for some time and was anxious that it be continued. After three weeks, he reported that the "Zoloft" was working and elected to stop taking the

Trexan since he "couldn't feel it do anything". He said he was feeling happy for the first time and that on his own he had stopped taking the Ativan except occasionally at night. One month later, he was not feeling quite as well and had resumed the full dose of Ativan.

He was instructed that he may have responded better to the Zoloft earlier because of the concurrent use of Trexan and he consented to restart it. One month later he reported his depression was gone, and had again, without prompting, discontinued the use of Ativan.

EXAMPLE 5

A chronically depressed, agoraphobic woman requested treatment for relief from severe suicidal depressive episodes. Due to her prominent phobic symptoms, she was started on imipramine 150–300 mg. at bedtime with equivocal results. A shift to Anafranil at similar doses resulted in a significantly better lifting of her mood but she was still quite impaired and subject to mood swings. One weekend she called and requested hospitalization due to very urgent wishes to kill herself. She happened to mention that Darvon would usually stop the urge to kill herself and rather than put her in hospital, she was given Darvon temporarily.

She was then started on Trexan 25 mg. in the morning with imipramine and three weeks later she felt "cured". Because of her concern about expense, she stopped the Trexan without telling her physician and presented again a few weeks later in a markedly depressed state despite continuing the imipramine. She was instructed to restart the Trexan and after several weeks she had an enormously improved mood and a marked reduction in her agoraphobic symptoms. In this lady, concurrent antidepressant with naltrexone was necessary to prevent likelihood of losing the patient to suicide or a return of severe depression.

EXAMPLE 6

A fifty-some year old man with recurrent episodes of depression and explosive rage was being treated with imipramine for some three months prior to being admitted to the hospital. He was already tying the rope around his neck when the police grabbed him. Three weeks after adding Trexan at 25 mg. in the morning to imipramine 175 mg. at bedtime, he began to describe a lifting of his depression and irritability and became quite social and lively.

EXAMPLE 7

A woman in her mid-thirties who had a leaking aneurysm requiring destructive brain surgery and relearning to speak, was treated. She had a lifelong history of depression and had been deeply depressed when seen. Treatment with 175 mg. of nortriptyline (Pamelor) for many months had resulted in equivocal improvement. After four weeks of Trexan 25 mg. in the morning with Pamelor, she began a marked and sustained remission of depression described by the patient as the best ever.

EXAMPLE 8

An operating room nurse with a bipolar depression which resisted tricyclics, a-typical antidepressants, and lithium,

alone, requested treatment. She was taking 600 mg. of Tegretal at bedtime when started on Trexan and was only taking the Tegretal to sleep. She had no antidepressant effect. She was then started on 50 mg. of Trexan with Tegretal and she slept for three days. She was instructed to dissolve the Trexan in water and take gradually increasing doses beginning with less than 2 mg. per day. She was able to increase to 25 mg. daily and after several months became almost hypomanic, requiring periodic discontinuation of the Trexan to avoid becoming giddy on the job. She reported that it was the first medicine combination she had taken that improved her mood reliably.

Tegretal is a tricyclic but an anticonvulsant/antimanic rather than antidepressant.

EXAMPLE 9

It is expected that the patient of Example 8, above, would improve even further if her treatment with Tegretal plus Trexan (25 mg.) was supplemented or replaced with treatment administering lithium plus 25 mg. Trexan. This latter combination would solve her problems dosing herself with Tegretal and Trexan intermittently correct her excess giddiness or mania, while preventing depressive episodes.

What is claimed is:

1. A method of treating depression associated with alcoholism, comprising administering to a patient a pharmacologically effective dose of an opioid antagonist having a pentacyclic nucleus structurally analogous to naltrexone, naloxone, and nalmefene, and a phatmacologically effective dose of an antidepressant compound selected from the group consisting of a serotonin reuptake inhibitor, a tricyclic antidepressant, an atypical antidepressant, and lithium, their pharmacologically effective salts and esters, or combinations thereof.

2. The method of claim **1**, wherein said opioid antagonist is selected from the group consisting of naltrexone hydrochloride, nalmefene, and the salt and esters of nalmefene.

3. The method of claim **1**, wherein the pharmacologically effective dose of said opioid antagonist is a molar equivalent weight to 25 mg. of naltrexone hydrochloride.

4. The method of claim **1**, wherein the pharmacologically effective dose of said opioid antagonist is a molar equivalent weight to 10 mg. of naltrexone hydrochloride.

5. The method of claim **1** wherein said opioid antagonist and said antidepressant compound are administered using a pharmaceutically acceptable carrier.

6. The method of claim **1**, wherein said antidepressant compound is selected from the group consisting of bupropion, sertraline, fluoxetine, paroxetine, trazodone, and their pharmacologically salts and ester, and combinations thereof.

7. The method of claim **1**, wherein said depressed patient is concomitantly being treated for a disorder selected from the group consisting of anxiety, mania, and convulsive disorder, wherein said anxiety disorder is being treated with a benzodiazepine compound, said mania is being treated with lithium and said convulsive disorder is being treated with an anticonvulsive active compound.

* * * * *

PTO/SB/51 (12-97)
Approved for use through 9/30/00 OMB 0651-0033
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

REISSUE APPLICATION DECLARATION BY THE INVENTOR

Docket Number (Optional)
14127.0001U1

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are stated below next to my name.
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is described and claimed **in patent number** 6,034,091 , **granted** March 7, 2000 , **and for which a** reissue patent is sought on the invention entitled Method for Treating Emotional or Mental Illness and Emotional or Mental Illness Concomitant with Seizures ,
the specification of which

[X] **is attached hereto.**

[ ] **was filed on** _____ **as reissue application number** ___ / _____
and was amended on _____ .
(If applicable)

I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.
I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.
I verily believe the original patent to be wholly or partly inoperative or invalid, for the reasons described below. (Check all boxes that apply.)

[ ] by reason of a defective specification or drawing.

[X] by reason of the patentee claiming more or less than he had the right to claim in the patent.

[X] by reason of other errors.

At least one error upon which reissue is based is described as follows:

The failure to include claims of proper scope to provoke an interference in the original patent application.

PTO/SB/51 (12-97)
Approved for use through 9/30/00. OMB 0651-0033
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(REISSUE APPLICATION DECLARATION BY THE INVENTOR, page 2)

Docket Number (Optional)
14127.0001U1

All errors corrected in this reissue application arose without any deceptive intention on the part of the applicant. **As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute** this application and transact all business in the Patent and Trademark Office connected therewith.

Name(s)	Registration Number
William R. Johnson	32,875

Correspondence Address: Direct all communications about the application to:

☒ Customer Number [ ] → Place Customer Number Bar Code Label Here 23859 PATENT TRADEMARK OFFICE

OR

Type Customer Number here

☐ Firm or Individual Name					
Address					
Address					
City		State		ZIP	
Country					
Telephone		Fax			

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this declaration is directed.

Full name of sole or first inventor (given name, family name)
Lee G. Dante

Inventor's signature Lee G. Dante

Residence
321 Berkeley Road

Date 9/18/00

Post Office Address
Merrion Station, PA 19066

Citizenship
U.S.A.

Full name of second joint inventor (given name, family name)

Inventor's signature

Date

Residence

Citizenship

Post Office Address

Full name of third joint inventor (given name, family name)

Inventor's signature

Date

Residence

Citizenship

Post Office Address

☐ Additional joint inventors are named on separately numbered sheets attached hereto.

1995 PDR same as 1993 PDR for Prozac

sible complications of sudden steroid

ncy—Safe use of Nalfon during pregnancy not been established; therefore, administ- ant patients and nursing mothers is not reproduction studies have been performed in When fenoprofen was given to rats during continued until the time of labor, parturition similar results have been found with other ti-inflammatory drugs that inhibit prosta- se.

ldren—Fenoprofen calcium is not recom- in children because documented clinical ex- en insufficient to establish safety and a suit- men in the pediatric age group.

EACTIONS

l studies for rheumatoid arthritis, osteoarthri- moderate pain and studies of pharmacokinet- were compiled from a checklist of potential ns, and the following data emerged. These rvations in 6,786 patients, including 188 ob- least 52 weeks. For comparison, data are also complaints received from the 266 patients lacebo in these same trials. During short-term lgesia, the incidence of adverse reactions was r than that seen in longer-term studies.

GREATER THAN 1%

al Relationship

ent—During clinical trials with Nalfon® Calcium, USP), the most common adverse reac- rointestinal in nature and occurred in 20.8% receiving Nalfon as compared to 16.9% of pa- g placebo. In descending order of frequency, included dyspepsia (10.3%, Nalfon, vs 2.3%, ea (7.7% vs 7.1%), constipation (7% vs 1.5%), % vs 1.9%), abdominal pain (2% vs 1.1%), and % vs 4.1%).

discontinued because of adverse gastrointesti- in less than 2% of patients during premarket-

m—The most frequent adverse neurologic headache (8.7% treated vs 7.5% placebo) and .5% vs 6.4%). Dizziness (6.5% vs 5.6%), tremor), and confusion (1.4% vs none) were noted less

discontinued in less than 0.5% of patients be- side effects during premarketing studies.

ndages—Increased sweating (4.6% vs 0.4%), % vs 0.8%), and rash (3.7% vs 0.4%) were re-

discontinued in about 1% of patients because of effect related to the skin during premarketing

s—Tinnitus (4.5% vs 0.4%), blurred vision), and decreased hearing (1.6% vs none) were

discontinued in less than 0.5% of patients be- erse effects related to the special senses during studies.

ular—Palpitations (2.5% vs 0.4%).

discontinued in about 0.5% of patients because cardiovascular reactions during premarketing

—Nervousness (5.7% vs 1.5%), asthenia (5.4% heral edema (5.0% vs 0.4%), dyspnea (2.8% vs (1.7% vs 1.5%), upper respiratory infection), and nasopharyngitis (1.2% vs none).

LESS THAN 1%

al Relationship

adverse reactions, occurring in less than 1% of reported in controlled clinical trials and vol- made since Nalfon® (Fenoprofen Calcium; initially marketed. The probability of a causal exists between Nalfon and these adverse reac-

m—Gastritis, peptic ulcer with/without per- rointestinal hemorrhage, anorexia, flatulence, and blood in the stool. Increases in alkaline phos- LDH, and SGOT, jaundice, and cholestatic hepatitis d (see Precautions).

y Tract—Dysuria, cystitis, hematuria, oliguria, uria, interstitial nephritis, nephrosis, and papil- (see Warnings).

—Angioedema (angioneurotic edema).

—Purpura, bruising, hemorrhage, thrombocy- plastic anemia, aplastic anemia, agranulocyto- penia.

—Anaphylaxis, urticaria, malaise, insomnia, ia.

LESS THAN 1%

ntly Unknown

reported either in clinical trials or spontane- d in circumstances in which a causal relation- be established. However, with these rarely ns, the possibility of such a relationship can- not be excluded. Therefore, these observations are listed to alert the physician.

Skin and Appendages—Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, and alopecia.

Digestive System—Aphthous ulcerations of the buccal mucosa, metallic taste, and pancreatitis.

Cardiovascular—Atrial fibrillation, pulmonary edema, electrocardiographic changes, and supraventricular tachycardia.

Nervous System—Depression, disorientation, seizures, and trigeminal neuralgia.

Special Senses—Burning tongue, diplopia, and optic neuritis.

Miscellaneous—Personality change, lymphadenopathy, mastodynia, and fever.

OVERDOSAGE

Signs and Symptoms—Symptoms of overdose appear within several hours and generally involve the gastrointestinal and central nervous systems. They include dyspepsia, nausea, vomiting, abdominal pain, dizziness, headache, ataxia, tinnitus, tremor, drowsiness, and confusion. Hyperpyrexia, tachycardia, hypotension, and acute renal failure may occur rarely following overdose. Respiratory depression and metabolic acidosis have also been reported following overdose with certain NSAIDs.

Treatment—To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Alkalinization of the urine, forced diuresis, peritoneal dialysis, hemodialysis, and charcoal hemoperfusion do not enhance systemic drug elimination.

DOSAGE AND ADMINISTRATION

Analgesia—For the treatment of mild to moderate pain, the recommended dosage is 200 mg every 4 to 6 hours, as needed.

Rheumatoid Arthritis and Osteoarthritis—The suggested dosage is 300 to 600 mg, 3 or 4 times a day. The dose should be tailored to the needs of the patient and may be increased or decreased depending on the severity of the symptoms. Dosage adjustments may be made after initiation of drug therapy or during exacerbations of the disease. Total daily dosage should not exceed 3,200 mg.

If gastrointestinal complaints occur, Nalfon® (Fenoprofen Calcium, USP) may be administered with meals or with milk. Although the total amount absorbed is not affected, peak blood levels are delayed and diminished.

Patients with rheumatoid arthritis generally seem to require larger doses of Nalfon than do those with osteoarthritis. The smallest dose that yields acceptable control should be employed.

Although improvement may be seen in a few days in many patients, an additional 2 to 3 weeks may be required to gauge the full benefits of therapy.

HOW SUPPLIED

(℞) Pulvules:

200 mg* (white and ocher) (No. 415)—(Identi-Code† H76) (RxPak‡ of 100) NDC 0777-0876-02

300 mg* (yellow and ocher) (No. 416)—(Identi-Code† H77) (RxPak‡ of 100) NDC 0777-0877-02; (500s) NDC 0777-0877-03

(℞) Tablets (DISTA imprinted on one side, NALFON on other side):

600 mg* (yellow, paracapsule-shaped, scored) (No. 1900)—(RxPak‡ of 100) NDC 0777-2159-02; (500s) NDC 0777-2159-03

* Equivalent to fenoprofen.

† Identi-Code® (formula identification code, Dista).

‡ All RxPaks (prescription packages, Dista) have safey closures.

Store at controlled room temperature, 59° to 86°F (15° to 30°C).

[121390]

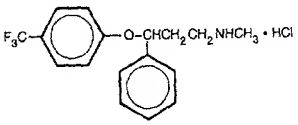
PROZAC® ℞

[*prō'zăk*]

(fluoxetine hydrochloride)

DESCRIPTION

Prozac® (Fluoxetine Hydrochloride) is an antidepressant for oral administration; it is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is designated (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride and has the empirical formula of $C_{17}H_{18}F_3NO \cdot HCl$. Its molecular weight is 345.79. The structural formula is:



Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/mL in water.

Each Pulvule® contains fluoxetine hydrochloride equivalent to 10 mg (32.3 μmol) or 20 mg (64.7 μmol) of fluoxetine. The Pulvules also contain F D & C Blue No. 1, gelatin, iron oxide, silicone, starch, titanium dioxide, and other inactive ingredients.

The oral solution contains fluoxetine hydrochloride equivalent to 20 mg/5 mL (64.7 μmol) of fluoxetine. It also contains alcohol 0.23%, benzoic acid, flavoring agent, glycerin, purified water, and sucrose.

CLINICAL PHARMACOLOGY

Pharmacodynamics—The antidepressant and antiobsessive-compulsive action of fluoxetine is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Studies at clinically relevant doses in man have demonstrated that fluoxetine blocks the uptake of serotonin into human platelets. Studies in animals also suggest that fluoxetine is a much more potent uptake inhibitor of serotonin than of norepinephrine.

Antagonism of muscarinic, histaminergic, and α_1-adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects of classical tricyclic antidepressant drugs. Fluoxetine binds to these and other membrane receptors from brain tissue much less potently in vitro than do the tricyclic drugs.

Absorption, Distribution, Metabolism, and Excretion:

Systemic Bioavailability—In man, following a single oral 40 mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours.

The Pulvule and oral solution dosage forms of fluoxetine are bioequivalent. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption inconsequentially. Thus, fluoxetine may be administered with or without food.

Protein Binding—Over the concentration range from 200 to 1,000 ng/mL, approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and α_1-glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated, but may be important (*see* Precautions).

Enantiomers—Fluoxetine is a racemic mixture (50/50) of *R*-fluoxetine and *S*-fluoxetine enantiomers. In animal models, both enantiomers are specific and potent serotonin uptake inhibitors with essentially equivalent pharmacologic activity. The *S*-fluoxetine enantiomer is eliminated more slowly and is the predominant enantiomer present in plasma at steady state.

Metabolism—Fluoxetine is extensively metabolized in the liver to norfluoxetine and a number of other, unidentified metabolites. The only identified active metabolite, norfluoxetine, is formed by demethylation of fluoxetine. In animal models, *S*-norfluoxetine is a potent and selective inhibitor of serotonin uptake and has activity essentially equivalent to *R*- or *S*-fluoxetine. *R*-norfluoxetine is significantly less potent than the parent drug in the inhibition of serotonin uptake. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

Clinical Issues Related to Metabolism/Elimination—The complexity of the metabolism of fluoxetine has several consequences that may potentially affect fluoxetine's clinical use.

Variability in Metabolism—A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme cytochrome PA450IID6. Such individuals are referred to as

Continued on next page

This product information was prepared in June 1994. Current information on these and other products of Dista Products Products Company may be obtained by direct inquiry to Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285, (800) 545-5979.

Dista—Cont.

"poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the tricyclic antidepressants. In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized S-fluoxetine at a slower rate and thus achieved higher concentrations of S-fluoxetine. Consequently, concentrations of S-norfluoxetine at steady state were lower. The metabolism of *R*-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative, nonsaturable pathways (non-IID6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit

Because fluoxetine's metabolism, like that of a number of other compounds including tricyclic and other selective serotonin antidepressants, involves the P450IID6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the tricyclic antidepressants) may lead to drug interactions (see Drug Interactions *under* Precautions).

Accumulation and Slow Elimination—The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use delayed attainment of steady state, even when a fixed dose is used. After 30 days of dosing at 40 mg/ day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/mL and norfluoxetine in the range of 72 to 258 ng/mL have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single-dose studies, because fluoxetine's metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days. Steady state levels after prolonged dosing are similar to levels seen at 4–5 weeks.

The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing is stopped, active drug substance will persist in the body for weeks (primarily depending on individual patient characteristics, previous dosing regimen, and length of previous therapy at discontinuation). This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of Prozac® (Fluoxetine Hydrochloride).

Liver Disease—As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared to the range of 2 to 3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared to the range of 7 to 9 days in normal subjects. This suggests that the use of fluoxetine in patients with liver disease must be approached with caution. If fluoxetine is administered to patients with liver disease, a lower or less frequent dose should be used (see Precautions *and* Dosage and Administration).

Renal Disease—In single dose studies, the pharmacokinetics of fluoxetine and norfluoxetine were similar among subjects with all levels of impaired renal function including anephric patients on chronic hemodialysis. However, with chronic administration, additional accumulation of fluoxetine or its metabolites (possibly including some not yet identified) may occur in patients with severely impaired renal function and use of a lower or less frequent dose is advised (see Precautions).

Age—The disposition of single doses of fluoxetine in healthy elderly subjects (greater than 65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of the drug, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥ 60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209.3 ± 85.7 ng/mL at the end of 6 weeks. No unusual age-associated pattern of adverse events was observed in those elderly patients.

Clinical Trials:

Depression—The efficacy of Prozac for the treatment of patients with depression (≥ 18 years of age) has been studied in 5- and 6-week placebo-controlled trials. Prozac was shown to be significantly more effective than placebo as measured by the Hamilton Depression Rating Scale (HAM-D). Prozac was also significantly more effective than placebo on the HAM-D subscores for depressed mood, sleep disturbance, and the anxiety subfactor.

Two 6-week controlled studies comparing Prozac, 20 mg, and placebo have shown Prozac, 20 mg daily, to be effective in the treatment of elderly patients (≥ 60 years of age) with depression. In these studies, Prozac produced a significantly higher rate of response and remission as defined respectively by a 50% decrease in the HAM-D score and a total endpoint HAM-D score of ≤ 7. Prozac was well tolerated and the rate of treatment discontinuations due to adverse events did not differ between Prozac (12%) and placebo (9%).

Obsessive Compulsive Disorder.—The effectiveness of Prozac for the treatment for obsessive compulsive disorder (OCD) was demonstrated in two 13-week, multicenter, parallel group studies (Studies 1 and 2) of adult outpatients who received fixed Prozac doses of 20, 40, or 60 mg/day (on a once a day schedule, in the morning) or placebo. Patients in both studies had moderate to severe OCD (DSM-III-R), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS, total score) ranging from 22 to 26. In Study 1, patients receiving Prozac experienced mean reductions of approximately 4 to 6 units on the YBOCS total score, compared to a 1-unit reduction for placebo patients. In Study 2, patients receiving Prozac experienced mean reductions of approximately 4 to 9 units on the YBOCS total score, compared to a 1-unit reduction for placebo patients. While there was no indication of a dose response relationship for effectiveness in Study 1, a dose response relationship was observed in Study 2, with numerically better responses in the 2 higher dose groups. The following table provides the outcome classification by treatment group on the CGI improvement scale for studies 1 and 2 combined.

Outcome Classification (%) on CGI Improvement Scale for Completers in Pool of Two OCD Studies

Classification	Placebo	Prozac		
		20 mg	40 mg	60 mg
Worse	8%	0%	0%	0%
No Change	64%	41%	33%	29%
Minimally Improved	17%	23%	28%	24%
Much Improved	8%	28%	27%	28%
Very Much Improved	3%	8%	12%	19%

Exploratory analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

INDICATIONS AND USAGE

Depression—Prozac® (Fluoxetine Hydrochloride) is indicated for the treatment of depression. The efficacy of Prozac was established in 5- and 6-week trials with depressed outpatients (≥ 18 years of age) whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder (see Clinical Trials *under* Clinical Pharmacology).

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The antidepressant action of Prozac in hospitalized depressed patients has not been adequately studied.

The effectiveness of Prozac in long-term use, that is, for more than 5 to 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Prozac for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Obsessive-Compulsive Disorder—Prozac is indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder (OCD), as defined in the DSM-III-R.–; ie, the obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of Prozac was established in 13-week trials with obsessive-compulsive outpatients whose diagnoses corresponded most closely to the DSM-III-R category of obsessive-compulsive disorder (see Clinical Trials *under* Clinical Pharmacology).

Obsessive-compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses, or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

The effectiveness of Prozac in long-term use, ie, for more than 13 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use Prozac for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see Dosage and Administration).

CONTRAINDICATIONS

Prozac® (Fluoxetine Hydrochloride) is contraindicated in patients known to be hypersensitive to it

Monoamine Oxidase Inhibitors—There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued fluoxetine and are then started on an MAOI Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, Prozac should not be used in combination with an MAOI, or within 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses [see Accumulation and Slow Elimination *under* Clinical Pharmacology]) should be allowed after stopping Prozac before starting an MAOI

WARNINGS

Rash and Possibly Allergic Events—During premarketing testing of more than 5,600 US patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

In premarketing clinical trials, 2 patients are known to have developed a serious cutaneous systemic illness In neither patient was there an unequivocal diagnosis, but 1 was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme Other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of Prozac, systemic events, possibly related to vasculitis, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Anaphylactoid events, including bronchospasm, angioedema, and urticaria alone and in combination, have been reported.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, Prozac should be discontinued.

PRECAUTIONS

General—Anxiety and Insomnia—Anxiety, nervousness, and insomnia were reported by 10% to 15% of patients treated with Prozac® (Fluoxetine Hydrochloride). These symptoms led to drug discontinuation in 5% of patients treated with Prozac.

In controlled clinical trials for obsessive-compulsive disorder, insomnia was reported in 30% of patients treated with Prozac and in 22% of patients treated with placebo. Anxiety was reported in 14% of patients treated with Prozac and in 7% of patients treated with placebo. These 2 symptoms led to drug discontinuation in 2% of patients treated with Prozac and no patients treated with placebo.

Altered Appetite and Weight—Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with Prozac.

In controlled clinical trials, approximately 9% of patients treated with Prozac experienced anorexia. This incidence is approximately sixfold that seen in placebo controls. A weight loss of greater than 5% of body weight occurred in 13% of patients treated with Prozac compared to 4% of placebo and 3% of patients treated with tricyclics. However, only rarely have patients discontinued treatment with Prozac because of weight loss.

In controlled clinical trials for OCD, 17% of patients treated with Prozac and 10% of patients treated with placebo reported anorexia. One *patient discontinued* treatment with Prozac because of anorexia.

Activation of Mania/Hypomania—During premarketing testing, hypomania or mania occurred in approximately 1%

of fluoxetine treated patients Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

Mania/hypomania was reported in 1% of patients treated with fluoxetine in controlled clinical OCD trials.

Seizures—Twelve patients among more than 6,000 evaluated worldwide in the course of premarketing development of fluoxetine experienced convulsions (or events described as possibly having been seizures), a rate of 0.2% that appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures

In controlled clinical trials for OCD, 1 patient treated with fluoxetine experienced a seizure

Suicide—The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

The Long Elimination Half-Lives of Fluoxetine and Its Metabolites—Because of the long elimination half-lives of the parent drug and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (*see* Clinical Pharmacology *and* Dosage and Administration)

Use in Patients With Concomitant Illness—Clinical experience with Prozac® (Fluoxetine Hydrochloride) in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately 3 beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients.

In patients with diabetes, Prozac may alter glycemic control. Hypoglycemia has occurred during therapy with Prozac, and hyperglycemia has developed following discontinuation of the drug. As is true with many other types of medication when taken concurrently by patients with diabetes, insulin and/or oral hypoglycemic dosage may need to be adjusted when therapy with Prozac is instituted or discontinued.

Interference With Cognitive and Motor Performance—Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Information for Patients —Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

- Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.
- Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs, or alcohol.
- Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.
- Patients should be advised to notify their physician if they are breast feeding an infant.
- Patients should be advised to notify their physician if they develop a rash or hives.

Laboratory Tests —There are no specific laboratory tests recommended.

Drug Interactions —As with all drugs, the potential for interaction by a variety of mechanisms (eg, pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc) is a possibility (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Drugs Metabolized by P450IID6—Approximately 7% of the normal population has a genetic defect that leads to reduced levels of activity of the cytochrome P450 isoenzyme P450IID6. Such individuals have been referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and tricyclic antidepressants. Many drugs, such as most antidepressants including fluoxetine and other selective uptake inhibitors of serotonin, are metabolized by this isoenzyme; thus, both the pharmacokinetic properties and relative proportion of metabolites are altered in poor metabolizers. However, for fluoxetine and its metabolite the sum of the plasma concentrations of the 4 active enantiomers is comparable between poor and extensive metabolizers (*see* Variability in Metabolism *under* Clinical Pharmacology).

Fluoxetine, like other agents that are metabolized by P450IID6, inhibits the activity of this isoenzyme, and thus may make normal metabolizers resemble "poor metabolizers." Therapy with medications that are predominantly metabolized by the P450IID6 system and that have a relatively narrow therapeutic index (*see* list below), should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or have taken it in the previous 5 weeks. Thus, his/her dosing requirements resemble those of "poor metabolizers." If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by P450IID6, the need for decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (eg, flecainide, vinblastine, carbamazepine, and tricyclic antidepressants).

Tryptophan—Five patients receiving Prozac® (Fluoxetine Hydrochloride) in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monoamine Oxidase Inhibitors—*See* Contraindications.

Other Antidepressants—There have been greater than 2-fold increases of previously stable plasma levels of other antidepressants when Prozac has been administered in combination with these agents (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Lithium—There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity have been reported. Lithium levels should be monitored when these drugs are administered concomitantly.

Diazepam Clearance—The half-life of concurrently administered diazepam may be prolonged in some patients (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Phenytoin—Patients on stable doses of phenytoin have developed elevated plasma phenytoin concentrations and clinical phenytoin toxicity following initiation of concomitant fluoxetine treatment.

Potential Effects of Coadministration of Drugs Tightly Bound to Plasma Proteins—Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (eg, Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound fluoxetine by other tightly bound drugs (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

CNS Active Drugs—The risk of using Prozac in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Prozac and such drugs is required (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Electroconvulsive Therapy—There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

Carcinogenesis, Mutagenesis, Impairment of Fertility —There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for 2 years at levels equivalent to approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively produced no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies conducted in rats at doses of approximately 5 and 9 times the maximum human dose (80 mg) indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted, but this was probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy —Teratogenic Effects —Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses 9 and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus due to Prozac® (Fluoxetine Hydrochloride). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery —The effect of Prozac on labor and delivery in humans is unknown

Nursing Mothers —Because Prozac is excreted in human milk, nursing while on Prozac is not recommended In 1 breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL The concentration in the mother's plasma was 295.0 ng/mL No adverse effects on the infant were reported. In another case, an infant nursed by a mother on Prozac developed crying, sleep disturbance, vomiting, and watery stools. The infant's plasma drug levels were 240 ng/mL of fluoxetine and 208 ng/mL of norfluoxetine on the second day of feeding

Usage in Children —Safety and effectiveness in children have not been established.

Usage in the Elderly —Evaluation of patients over the age of 60 who received Prozac 20 mg daily revealed no unusual pattern of adverse events relative to the clinical experience in younger patients However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs (*see* Age *under* Clinical Pharmacology).

Hyponatremia —Several cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported. The hyponatremia appeared to be reversible when Prozac was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted. In a placebo-controlled, double-blind trial, 10 of 313 fluoxetine patients and 6 of 320 placebo recipients had a lowering of serum sodium below the reference range; this difference was not statistically significant. The lowest observed concentration was 129 mmol/L. The observed decreases were not clinically significant

Platelet Function —There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking fluoxetine While there have been reports of abnormal bleeding in several patients taking fluoxetine, it is unclear whether fluoxetine had a causative role.

ADVERSE REACTIONS

Commonly Observed —The most commonly observed adverse events associated with the use of Prozac® (Fluoxetine Hydrochloride) and not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including anxiety, nervousness, and insomnia, drowsiness and fatigue or asthenia; tremor, sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea, and dizziness or lightheadedness.

In controlled clinical trials for OCD using fixed doses of 20, 40, or 60 mg daily, adverse events observed at an incidence of at least 5% for Prozac and for which the incidence was approximately twice or more the incidence among placebo-treated patients included: somnolence, anxiety, tremor, nausea, dyspepsia, gastrointestinal disorder, vasodilatation, dry mouth, sweating, rash, abnormal vision, yawn, decreased libido, and abnormal ejaculation

Associated With Discontinuation of Treatment —Fifteen percent of approximately 4,000 patients who received Prozac in US premarketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3 0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

In controlled clinical trials for OCD, 12% of patients treated with Prozac discontinued treatment due to adverse events The most common events were anxiety (2%) and rash/urticaria (2%)

Incidence in Controlled Clinical Trials —

Depression—Table 1 enumerates adverse events that occurred at a frequency of 1% or more among patients treated with Prozac who participated in controlled trials comparing Prozac with placebo.

Obsessive-Compulsive Disorder—Table 2 enumerates adverse events that occurred at a frequency of 2% or more among patients on Prozac who participated in controlled trials comparing Prozac with placebo in the treatment of OCD.

The prescriber should be aware that the figures in Tables 1 and 2 cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in

Continued on next page

This product information was prepared in June 1994. Current information on these and other products of Dista Products Products Company may be obtained by direct inquiry to Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285, (800) 545-5979.

Dista—Cont.

the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied

[See Table 1 below]
[See Table 2 on next page]

Other Events Observed During Premarketing Evaluation of Prozac® (Fluoxetine Hydrochloride)—During clinical testing in the US, multiple doses of Prozac were administered to approximately 5,600 subjects Untoward events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (ie, reduced) number of standardized event categories.

In the tabulations that follow, a standard COSTART Dictionary terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 5,600 individuals exposed to Prozac who experienced an event of the type cited on at least 1 occasion while receiving Prozac All reported events are included except those already listed in Table 1, those COSTART terms so general as to be uninformative, and those events where a drug cause was remote It is important to emphasize that, although the events reported did occur during treatment with Prozac, they were not necessarily caused by it.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions frequent adverse events are defined as those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole—*Frequent:* chills; *Infrequent:* chills and fever, cyst, face edema, hangover effect, jaw pain, malaise, neck pain, neck rigidity, and pelvic pain; *Rare:* abdomen enlarged, cellulitis, hydrocephalus, hypothermia, LE syndrome, moniliasis, and serum sickness.

Cardiovascular System—*Infrequent:* angina, pectoris, arrhythmia, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, and tachycardia; *Rare:* AV block first degree, bradycardia, bundle branch block, cerebral ischemia, myocardial infarct, thrombophlebitis, vascular headache, and ventricular arrhythmia.

Digestive System—*Frequent:* increased appetite; *Infrequent:* aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, liver function tests abnormal, melena, stomatitis, thirst; *Rare:* bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hematemesis, hepatitis, hepatomegaly, hyperchlorhydria, increased salivation, jaundice, liver tenderness, mouth ulceration, salivary gland enlargement, stomach ulcer, tongue discoloration, and tongue edema

Endocrine System—*Infrequent* hypothyroidism, *Rare:* goiter and hyperthyroidism.

Hemic and Lymphatic System—*Infrequent:* anemia and lymphadenopathy; *Rare:* bleeding time increased, blood dyscrasia, leukopenia, lymphocytosis, petechia, purpura, sedimentation rate increased, and thrombocythemia.

Metabolic and Nutritional—*Frequent:* weight loss, *Infrequent:* generalized edema, hypoglycemia, peripheral edema, and weight gain; *Rare:* dehydration, gout, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemic reaction, hypokalemia, hyponatremia, and iron deficiency anemia

Musculoskeletal System—*Infrequent:* arthritis, bone pain, bursitis, tenosynovitis, and twitching; *Rare:* bone necrosis, chondrodystrophy, muscle hemorrhage, myositis, osteoporosis, pathological fracture, and rheumatoid arthritis.

Nervous System—*Frequent:* abnormal dreams and agitation; *Infrequent:* abnormal gait, acute brain syndrome, akathisia, amnesia, apathy, ataxia, buccoglossal syndrome, CNS stimulation, convulsion, delusions, depersonalization, emotional lability, euphoria, hallucinations, hostility, hyperkinesia, hypesthesia, incoordination, libido increased, manic reaction, neuralgia, neuropathy, paranoid reaction, psychosis, and vertigo; *Rare:* abnormal electroencephalogram, antisocial reaction, chronic brain syndrome, circumoral paresthesia, CNS depression, coma, dysarthria, dystonia, extrapyramidal syndrome, hypertonia, hysteria, myoclonus, nystagmus, paralysis, reflexes decreased, stupor, and torticollis

Respiratory System—*Frequent* bronchitis, rhinitis, and yawn; *Infrequent.* asthma, epistaxis, hiccup, hyperventilation, and pneumonia, *Rare* apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibrosis/alveolitis, and pleural effusion.

Skin and Appendages—*Infrequent:* acne, alopecia, contact dermatitis, dry skin, herpes simplex, maculopapular rash, and urticaria; *Rare:* eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutism, psoriasis, purpuric rash, pustular rash, seborrhea, skin discoloration, skin hypertrophy, subcutaneous nodule, and vesiculobullous rash.

Special Senses—*Infrequent:* amblyopia, conjunctivitis, ear pain, eye pain, mydriasis, photophobia, and tinnitus; *Rare:* blepharitis, cataract, corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, ptosis, strabismus, and taste loss.

Urogenital System—*Infrequent:* abnormal ejaculation, amenorrhea, breast pain, cystitis, dysuria, fibrocystic breast, impotence, leukorrhea, menopause, menorrhagia, ovarian disorder, urinary incontinence, urinary retention, urinary urgency, urination impaired, and vaginitis; *Rare.* abortion, albuminuria, breast enlargement, dyspareunia, epididymitis, female lactation, hematuria, hypomenorrhea, kidney calculus, metrorrhagia, orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral pain, urethritis, urinary tract disorder, urolithiasis, uterine hemorrhage, uterine spasm, and vaginal hemorrhage.

Postintroduction Reports—Voluntary reports of adverse events temporally associated with Prozac that have been received since market introduction, that are not listed above, and that may have no causal relationship with the drug include the following: aplastic anemia, cerebral vascular accident, confusion, dyskinesia (including, for example, a case of buccal-lingual-masticatory syndrome with involuntary tongue protrusion reported to develop in a 77-year-old female after 5 weeks of fluoxetine therapy and which completely resolved over the next few months following drug discontinuation), eosinophilic pneumonia, hyperprolactinemia, immune-related hemolytic anemia, movement disorders developing in patients with risk factors including drugs associated with such events and worsening of preexisting movement disorders, neuroleptic malignant syndrome-like events, pancreatitis, pancytopenia, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal, and violent behaviors.

TABLE 1—TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

Body System/ Preferred Term*	Percentage of Patients Reporting Event Prozac (N=1,730)	Placebo (N=799)	Body System/ Preferred Term*	Percentage of Patients Reporting Event Prozac (N=1,730)	Placebo (N=799)
Nervous			**Body as a Whole**		
Headache	20 3	15 5	Asthenia	4.4	1.9
Nervousness	14 9	8.5	Infection, viral	3 4	3.1
Insomnia	13.8	7.1	Pain, limb	1 6	1 1
Drowsiness	11 6	6.3	Fever	1.4	—
Anxiety	9 4	5.5	Pain, chest	1.3	1 1
Tremor	7 9	2.4	Allergy	1.2	1.1
Dizziness	5 7	3.3	Influenza	1 2	1 5
Fatigue	4.2	1.1	**Respiratory**		
Sedated	1 9	1 3	Upper respiratory infection	7.6	6.0
Sensation disturbance	1.7	2.0	Flu-like syndrome	2.8	1.9
Libido decreased	1.6	—	Pharyngitis	2.7	1.3
Lightheadedness	1.6	—	Nasal congestion	2.6	2.3
Concentration, decreased	1 5	—	Headache, sinus	2.3	1 8
Digestive			Sinusitis	2.1	2.0
Nausea	21 1	10.1	Cough	1.6	1.6
Diarrhea	12 3	7.0	Dyspnea	1.4	—
Mouth dryness	9 5	6.0	**Cardiovascular**		
Anorexia	8.7	1.5	Hot flushes	1.8	1.0
Dyspepsia	6 4	4.3	Palpitations	1.3	1.4
Constipation	4.5	3 3	**Musculoskeletal**		
Pain, abdominal	3 4	2 9	Pain, back	2 0	2.4
Vomiting	2 4	1.3	Pain, joint	1.2	1.1
Taste change	1 8	—	Pain, muscle	1.2	1.0
Flatulence	1 6	1.1	**Urogenital**		
Gastroenteritis	1 0	1.4	Menstruation, painful†	2.6	2.1
Skin and Appendages			Sexual dysfunction	1.9	—
Sweating, excessive	8 4	3.8	Impotence, sexual‡	1.7	0.4
Rash	2 7	1 8	Frequent micturition	1.6	—
Pruritus	2 4	1.4	Urinary tract infection	1.2	—
			Special Senses		
			Vision disturbance	2.8	1.8

* Events reported by at least 1% of patients treated with Prozac are included.
† Denominator used was females only (N = 1,210 Prozac; N = 523 placebo).
‡ Denominator used was males only (N = 520 Prozac; N = 276 placebo).
—Incidence less than 1%.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class—Prozac® (Fluoxetine Hydrochloride) is not a controlled substance.

Physical and Psychological Dependence—Prozac has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the premarketing clinical experience with Prozac did not reveal any tendency for a withdrawal syndrome or any drug seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Prozac (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience—As of December 1987, there were 2 deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1,800 mg of fluoxetine and an undetermined amount of maprotiline. Plasma concentrations of fluoxetine and maprotiline were 4.57 mg/L and 4.18 mg/L, respectively. A second death involved 3 drugs yielding plasma concentrations as follows: fluoxetine, 1.93 mg/L; norfluoxetine, 1.10 mg/L; codeine, 1.80 mg/L; temazepam, 3.80 mg/L.

One other patient who reportedly took 3,000 mg of fluoxetine experienced 2 grand mal seizures that remitted spontaneously without specific anticonvulsant treatment (*see* Management of Overdose). The actual amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation. Except for the 2 deaths noted above, all other overdose cases recovered without residua.

Since introduction, reports of death attributed to overdosage of fluoxetine alone have been extremely rare.

Animal Experience—Studies in animals do not provide precise or necessarily valid information about the treatment of human overdose. However, animal experiments can provide useful insights into possible treatment strategies.

The oral median lethal dose in rats and mice was found to be 452 and 248 mg/kg respectively. Acute high oral doses produced hyperirritability and convulsions in several animal species.

Among 6 dogs purposely overdosed with oral fluoxetine, 5 experienced grand mal seizures. Seizures stopped immediately upon the bolus intravenous administration of a standard veterinary dose of diazepam. In this short term study, the lowest plasma concentration at which a seizure occurred was only twice the maximum plasma concentration seen in humans taking 80 mg/day, chronically.

In a separate single-dose study, the ECG in dogs given high doses did not reveal prolongation of the PR, QRS, or QT intervals. Tachycardia and an increase in blood pressure were observed. Consequently, the value of the ECG in predicting cardiac toxicity is unknown. Nonetheless, the ECG should ordinarily be monitored in cases of human overdose (*see* Management of Overdose).

Management of Overdose—Establish and maintain an airway; ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdose.

Cardiac and vital signs monitoring is recommended, along with general symptomatic and supportive measures. Based on experience in animals, which may not be relevant to humans, fluoxetine-induced seizures that fail to remit spontaneously may respond to diazepam.

There are no specific antidotes for Prozac® (Fluoxetine Hydrochloride).

Due to the large volume of distribution of Prozac, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

In managing overdosage, consider the possibility of multiple drug involvement. A specific caution involves patients taking or recently having taken fluoxetine who might ingest by accident or intent, excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (*see* Other Antidepressants *under* Precautions).

The physician should consider contacting a poison control center on the treatment of any overdose. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*.

DOSAGE AND ADMINISTRATION

Depression:

Initial Treatment—In controlled trials used to support the efficacy of fluoxetine, patients were administered morning doses ranging from 20 mg to 80 mg/day. Studies comparing fluoxetine 20, 40, and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory antidepressant response. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose.

A dose increase may be considered after several weeks if no clinical improvement is observed. Doses above 20 mg/day may be administered on a once a day (morning) or b.i.d. schedule (ie, morning and noon) and should not exceed a maximum dose of 80 mg/day.

As with other antidepressants, the full antidepressant effect may be delayed until 4 weeks of treatment or longer.

As with many other medications, a lower or less frequent dosage should be used in patients with renal and/or hepatic impairment. A lower or less frequent dosage should also be considered for patients, such as the elderly (*see* Usage in the Elderly *under* Precautions), with concurrent disease or on multiple medications.

Maintenance/Continuation/Extended Treatment—There is no body of evidence available to answer the question of how long the patient treated with fluoxetine should remain on it. It is generally agreed among expert psychopharmacologists (circa 1987) that acute episodes of depression require several months or longer of sustained pharmacologic therapy. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Obsessive-Compulsive Disorder:

Initial Treatment—In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of obsessive-compulsive disorder, patients were administered fixed daily doses of 20, 40, or 60 mg of fluoxetine or placebo (*see* Clinical Trials *under* Clinical Pharmacology). In one of these studies, no dose response relationship for effectiveness was demonstrated. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose. Since there was a suggestion of a possible dose response relationship for effectiveness in the second study, a dose increase may be considered after several weeks if insufficient clinical improvement is observed. The full therapeutic effect may be delayed until 5 weeks of treatment or longer.

Doses above 20 mg/day may be administered on a once a day (ie, morning) or b.i.d. schedule (ie, morning and noon). A dose range of 20 to 60 mg/day is recommended, however, doses of up to 80 mg/day have been well tolerated in open studies of OCD. The maximum fluoxetine dose should not exceed 80 mg/day.

As with the use of Prozac in depression, a lower or less frequent dosage should be used in patients with renal and/or hepatic impairment. A lower or less frequent dosage should also be considered for patients, such as the elderly (*see* Usage in the Elderly *under* Precautions), with concurrent disease or on multiple medications.

Maintenance/Continuation Treatment—While there are no systematic studies that answer the question of how long to continue Prozac, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of Prozac after 13 weeks has not been documented in controlled trials, patients have been continued in therapy under double-blind conditions for up to an additional 6 months without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment.

TABLE 2
TREATMENT EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS FOR OBSESSIVE-COMPULSIVE DISORDER

Body System/ Preferred Team*	Percent of Patients Reporting Event: Prozac (N=264)	Placebo (N=89)	Body System/ Preferred Team	Percent of Patients Reporting Event: Prozac (N=264)	Placebo (N=89)
Nervous			**Body as a Whole**		
Insomnia	30	22	Headache	33	24
Somnolence	17	7	Asthenia	15	10
Anxiety	14	7	Flu syndrome	10	7
Dizziness	13	11	Pain	6	4
Libido, decreased	11	2	Injury, accidental	4	2
Tremor	9	1	Surgical procedure	3	—
Abnormal dreams	5	2	Chest pain	3	1
Thinking, abnormal	4	2	Allergic reaction	3	—
Sleep disorder	3	1	Fever	2	1
Confusion	2	1	**Respiratory**		
Myoclonus	2	—	Pharyngitis	11	9
Agitation	2	1	Yawn	7	—
Amnesia	2	1	Sinusitis	5	2
Digestive			Cough, increased	3	2
Nausea	27	13	**Cardiovascular**		
Diarrhea	18	13	Vasodilatation	5	—
Anorexia	17	10	Palpitations	2	1
Dry mouth	12	3	**Musculoskeletal**		
Dyspepsia	10	4	Myalgia	5	4
Gastrointestinal disorder	6	1	Arthralgia	3	2
Melena	2	—	**Urogenital**		
Skin and Appendages			Urinary freqeuncy	4	1
Sweating	7	—	Abnormal ejaculation†	7	—
Rash	6	3	**Hemic and Lymphatic**		
Pruritus	3	1	Lymphadenopathy	2	—
Acne	2	1	**Metabolic and Nutritional**		
			Weight loss	5	3
			Special Senses		
			Ambylopia	3	1
			Abnormal vision	2	—
			Taste perversion	2	1
			Tinnitus	2	—

* Events reported by at least 2% of patients treated with Prozac are included, except the following events which had an incidence on placebo ≥ Prozac: abdominal pain, back pain, constipation, depression, dysmenorrhea, flatulence, infection, menstrual disorder, nervousness, rhinitis, tooth disorder, and twitching.
† Denominator used was males only (N=116 Prozac; N=43 placebo).
— Adverse event not reported by placebo-treated patients.

HOW SUPPLIED

(℞) Pulvules: 10 mg* green and gray (No. 3104)—(100s) NDC 0777-3104-02
20 mg* green and off-white (No. 3105)—(100s) NDC 0777-3105-02; (ID†100)NDC 0777-3105-33
(℞) Liquid, Oral Solution: 20 mg*/5 mL, mint flavor (M-5120‡)—(120 mL) NDC 0777-5120-58
* Fluoxetine base equivalent.
† Identi-Dose® (unit dose medication, Dista).
‡ Dispense in a tight, light-resistant container.
Store at controlled room temperature, 59° to 86°F (15° to 30°C).

Animal Toxicology: Phospholipids are increased in some tissues of mice, rats, and dogs given fluoxetine chronically. This effect is reversible after cessation of fluoxetine treatment. Phospholipid accumulation in animals has been observed with many cationic amphiphilic drugs, including fenfluramine, imipramine, and ranitidine. The significance of this effect in humans is unknown.

[031494]

Shown in Product Identification Guide, page 309

[See table on next page.]

CARMOL® 10 OTC
10% urea lotion.
Moisturizer for total body dry skin care

COMPOSITION

A greaseless deep moisturizing formula to help keep skin soft and supple. Urea 10% is a blend of purified water, stearic acid, isopropyl palmitate, propylene glycol dipelargonate, PEG-8 dioleate, propylene glycol, PEG 8 distearate, cetyl alcohol, sodium laureth sulfate, trolamine, carbomer 940, xanthan gum, scented with hypoallergenic fragrance. Contains no preservatives, lanoline or mineral oil.

HOW SUPPLIED

6 fl. oz. bottle, NDC #0482-2650-10

Continued on next page

United States Patent [19]

Dante

[54] **METHOD FOR TREATING EMOTIONAL OR MENTAL ILLNESS AND EMOTIONAL OR MENTAL ILLNESS CONCOMITANT WITH SEIZURES**

[75] Inventor: **Lee G. Dante**, Merion Station, Pa.

[73] Assignee: **John S. Nagle**, San Diego, Calif.

[21] Appl. No.: **09/165,549**

[22] Filed: **Oct. 2, 1998**

Related U.S. Application Data

[60] Continuation of application No. 08/755,795, Aug. 28, 1996, Pat. No. 5,856,332, which is a division of application No. 08/560,820, Nov. 20, 1995, Pat. No. 5,817,665, which is a division of application No. 08/031,096, Mar. 2, 1993, Pat. No. 5,512,593.

[51] **Int. Cl.**[7] **A61K 31/44**; A61K 31/495; A61K 31/445; A61K 31/135; A61K 33/14

[52] **U.S. Cl.** **514/282**; 514/253; 514/321; 514/649; 514/651; 514/657; 424/677; 424/722

US006034091A

[11] **Patent Number: 6,034,091**

[45] **Date of Patent: Mar. 7, 2000**

[58] **Field of Search** 514/282, 253, 514/321, 649, 651, 657; 424/677, 722

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,064,834 11/1991 Zimmerman et al. 514/279

Primary Examiner—William R. A. Jarvis
Attorney, Agent, or Firm—John S. Nagle, Esq.

[57] **ABSTRACT**

Disclosed herein is a method for treating depression associated with alcoholism in a patient comprising administering to the patient a pharmacologically effective dose of an opioid antagonist, and a pharmacologically effective dose of at least one drug compound selected from the group consisting of a tricyclic antidepressant, an a-typical antidepressant, and lithium.

7 Claims, No Drawings